

STRUCTURE AND SPECTRAL PROPERTIES OF  $\beta$ -CARBOLINES.  
PART 6.<sup>1</sup> REGIOSELECTIVITY OF CYCLOCONDENSATION OF  
SPIRO[PIPERIDINE-*m'*,1-(1,2,3,4-TETRAHYDRO- $\beta$ -CARBOLINES)]  
WITH ALDEHYDES

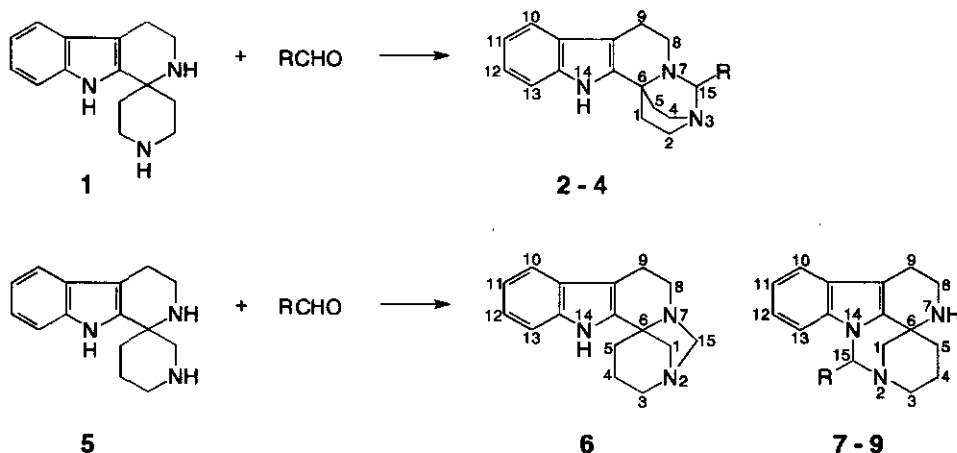
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**Abstract** - Cyclocondensation of spiro derivatives of 1,2,3,4-tetrahydro- $\beta$ -carbolines (**1**) and (**5**) with aldehydes was found to be a regioselective process. The structure of individual new ring systems, i.e. N-3,7 (**2-4**), N-2,7 (**6**) and N-2,14 (**7-9**) cyclocondensation products, was determined using <sup>1</sup>H nmr techniques.

In our previous papers we reported on the synthesis of new ring systems which contain a 1,2,3,4-tetrahydro- $\beta$ -carboline skeleton.<sup>1,2</sup> In order to expand our interest in preparing rigid systems which may serve as model ligands of the well defined geometry of serotonin receptors,<sup>3</sup> we decided to explore the reaction of two spirans (**1**) and (**5**) with aldehydes. A cyclocondensation of **1** with paraformaldehyde, benzaldehyde or o-chlorobenzaldehyde in an aprotic medium yielded bicyclic compounds (**2**), (**3**) and (**4**), respectively, as the only product of the reaction. A reaction of spiran (**5**) with paraformaldehyde under the same conditions resulted in a mixture of two isomers (**6**) and (**7**) (Scheme 1). A cyclocondensation at the N-2,7 atoms (**6**) occurred with a low yield, whereas a competitive

process which involved the N-2,14 atoms furnished isomer (7) as a major product. However, a reaction of 5 with aromatic aldehydes gave only the N-2,14 condensation products (8) and (9) (Table 1).



R: H (**2**, **7**);  $C_6H_5$  (**3**, **8**); 2-Cl- $C_6H_4$  (**4**, **9**)

**Scheme 1. General procedure:** A solution of **1** or **5** (240 mg, 1 mmol) and paraformaldehyde (2 mmol) or the appropriate aromatic aldehyde (1.1 mmol) in benzene (10 ml) was refluxed for 2-3 h. The reaction mixture was evaporated to dryness, and the residue was recrystallized from ethyl acetate (**2**), benzene (**3**), methanol (**4**), ethanol (**6**), ethanol/n-hexane (**7**), ether (**8**) or ether/n-hexane (**9**). The mixture of **6** and **7** was separated by a silica gel chromatography with chloroform/ethanol/triethylamine (7:2:1) as a mobile phase.

$^1H$  Nmr spectra of the aromatic region and chemical shifts of the C-15 methylene bridge protons (Table 2) have a strong diagnostic value for the structure determination of the investigated compounds.  $^1H$  Chemical shifts were assigned by correlation with the spectra of spirans (**1**) and (**5**),<sup>1</sup> and on the grounds of 1D nOe and 2D COSY experiments. The most spectacular difference in the spectra of **2-4** and **6-9** is the presence of the 14-NH resonance. The signal that is characteristic for structures (**2-4**) and (**6**) disappeared in spectra of **7-9** (Table 2). The 15- $H_2$  signals in compounds (**7-9**) were shifted downfield by

0.71-1.75 ppm, in relation to the position of those signals in structures (2-4) and (6), as a result of a deshielding effect of the indole nucleus.

**Table 1.** Physicochemical Data and Analyses of Compounds (2-4) and (6-9).

No.	mp (°C)	Yield (%)	Analysis (%), Calcd (Found)			M <sup>+</sup> (%) <sup>a</sup>
			C	H	N	
<b>2</b>	218-220	74	70.82 <sup>b</sup> (70.74)	7.80 <sup>b</sup> (8.02)	15.48 <sup>b</sup> (15.50)	253 (100)
<b>3</b>	195-197 (decomp.)	86	80.21 (80.62)	7.04 (6.97)	12.76 (12.49)	329 (99)
<b>4</b>	220 (decomp.)	44	72.62 (72.51)	6.09 (5.97)	11.55 (11.42)	365 (31)
<b>6</b>	153-156	12	75.85 (75.72)	7.56 (7.44)	16.59 (16.26)	253 (20)
<b>7</b>	133-139 (decomp.)	82	75.85 (75.98)	7.56 (7.66)	16.59 (16.84)	253 (12)
<b>8</b>	168-170	53	80.21 (79.86)	7.04 (7.05)	12.76 (12.44)	329 (32)
<b>9</b>	146-148	36	72.61 (72.49)	6.09 (6.28)	11.55 (11.36)	365 (2)

<sup>a</sup>Electron impact mass spectra at 70 eV. <sup>b</sup>Analysis for monohydrate.

The aromatic 13-H resonance in **2-4** and **6** is insensitive to the C-15 substituents, whereas the same proton in compounds (**8**) and (**9**) is shielded by the C-15 aromatic substituents and its signal is shifted upfield by 0.39 and 0.81 ppm, respectively, in relation to **7**. A similar effect was observed for the 11-H resonance signal. Moreover, the shielding effect of the indole ring system reflects in a significant upfield shift of the 2'-H and 3'-H resonances in **8** and **9** in comparison with **3** and **4** (Table 2).

The 1D nOe difference measurements were also found useful for the structure determination. Irradiation of the 14-NH signal of **2** resulted in an increased intensity of

the 1- and 5-H<sup>ax</sup> signal, whereas irradiation of the 15-H<sub>2</sub> signal caused enhancement of the 7-H<sub>2</sub> resonance intensity. Contrariwise, irradiation of each of the 15-H<sub>2</sub> doublets in compound (7) increased the same 13-H resonance signal.

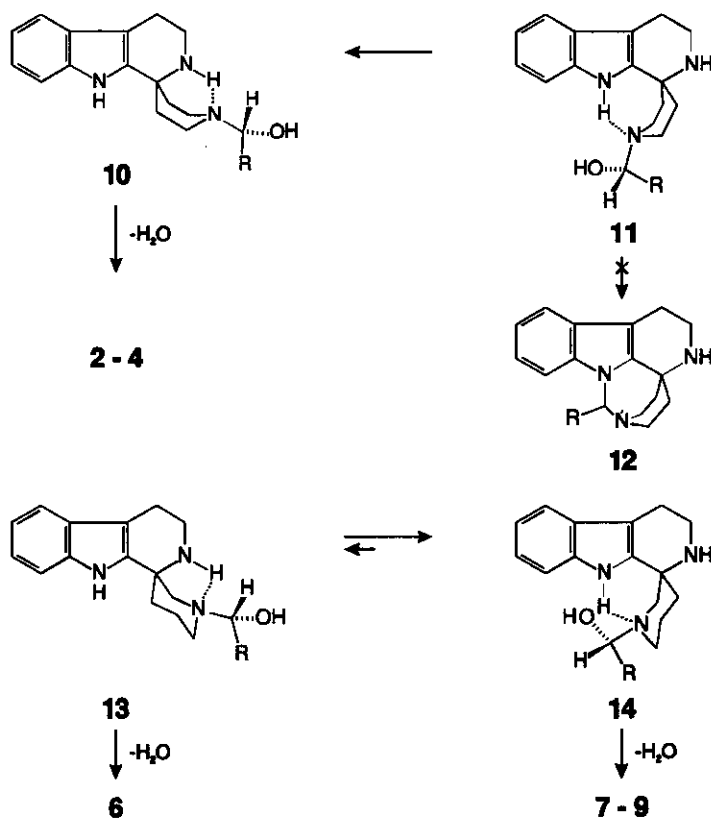
**Table 2.** <sup>1</sup>H Chemical Shifts (Aromatic Region and Methylene Bridge) of Compounds (2-4) and (6-9).<sup>4</sup>

Proton <sup>a</sup>	δ, ppm						
	2	3	4	6	7	8	9
10	7.48	7.51	7.50	7.51	7.44	7.53	7.51
11	7.09	7.11	7.11	7.11	7.04	6.94	6.90
12	7.14	7.16	7.16	7.15	7.09	7.04	7.07
13	7.30	<sup>b</sup>	7.32	7.31	7.17	6.78	6.36
14-NH	7.91	7.65	7.67	7.92			
15	3.88	4.43	4.71	<sup>c</sup>	<sup>d</sup>	6.18	6.23
2'		7.58				<sup>e</sup>	
3'		<sup>b</sup>	8.03			<sup>f</sup>	7.76
4'		<sup>b</sup>	7.30			<sup>f</sup>	7.40
5'		<sup>b</sup>	7.25			<sup>f</sup>	7.31
6'		7.68	7.40			<sup>e</sup>	7.56

<sup>a</sup>Numbering corresponds to that shown in Scheme 1. <sup>b</sup>7.28-7.39, m. <sup>c</sup>3.67 (1H, d, J = 9.3 Hz) and 4.29 (1H, d, J = 9.3 Hz). <sup>d</sup>4.81 (1H, d, J = 11.3 Hz) and 5.00 (1H, d, J = 11.3 Hz). <sup>e</sup>6.43-6.47, m. <sup>f</sup>7.09-7.15, m.

Both MAXIMIN2 and MNDO calculations<sup>5</sup> indicated that the N-2,14 (7-9) or N-3,14 (12) cyclocondensation products are more stable, by 3.7 - 9.9 kcal/mol, than their N-2,7 (6) or N-3,7 (2-4) counterparts. On the other hand, the applied conditions of the reaction (benzene, reflux) are characteristic for a kinetic control of the process. There are two basic

nitrogen atoms in spirans (**1**) and (**5**). The determined  $pK_a$  values of **1** are equal to  $9.69 \pm 0.09$  and  $5.94 \pm 0.07$  for N-3 and N-7 atoms, respectively.<sup>6</sup> The observed basicity-weakening effect of the N-7 atom in relation to the N-3 one is due to a steric crowding around the N-7 protonation center.<sup>3,7</sup> Therefore it is rational to assume that the N-3 and N-2 nucleophilic centers rather than the N-7 ones in spirans (**1**) and (**5**), respectively, attack the carbonyl group and form hemiaminals as intermediates (Scheme 2).



**Scheme 2.**

Recently we showed that a strong intramolecular hydrogen bond exists between the 14-NH and 2-N atoms of **5**, due to their favorable steric arrangement.<sup>1</sup> Contrariwise, there is no evidence for an intramolecular hydrogen bond in spiran (**1**).<sup>1</sup> Hence it seems obvious that the intramolecular hydrogen bond should stabilize some conformations of the hemiaminal

intermediates. In fact, among the possible structures of **10**, **11**, **13** and **14**, only **10** and **14** may be significantly stabilized by the intramolecular hydrogen bond which forms the most preferred six-membered ring. In this respect, structure (**13**), which contains a five-membered ring, is less favorable than **14**. Furthermore, structure (**11**) is definitely unfavorable, since the intramolecular hydrogen bond requires formation of a seven-membered ring. Moreover, an additional steric repulsion between the RCH(OH)-substituent and the indole fragment in **11** may also prevent formation of the N-3,14 hydrogen bond.

Summing up, the above conclusions are fully consistent with the observed regioselectivity of cyclocondensation of **1** and **5** with aldehydes.

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3. A. J. Bojarski, M. T. Cegła, S. Charakchieva-Minol, M. J. Mokrosz, M. Maćkowiak, S. Misztal, and J. L. Mokrosz, *Pharmazie*, 1993, **48**, 289.
4.  $^1\text{H}$  nmr spectra were measured on a Bruker 500 (500 MHz) instrument in  $\text{CDCl}_3$  solutions downfield from TMS.  $^1\text{H}$  Chemical shifts of the diazapro[5.5]undecane skeleton are as follow:  
**2**:  $\delta$  1.85 (2H, ddd,  $J = 12.6, 10.2,$  and  $5.0$  Hz, 1- and 5- $\text{H}^{\text{ax}}$ ), 2.02-2.09 (2H, m, 1- and 5- $\text{H}^{\text{eq}}$ ), 2.79-2.84 (4H, m, 8- and 9- $\text{H}_2$ ), 2.99 (2H, ddd,  $J = 13.5, 10.2,$  and  $5.3$  Hz, 2- and 4- $\text{H}^{\text{ax}}$ ), 3.22 (2H, ddd,  $J = 13.4, 10.5,$  and  $5.0$  Hz, 2- and 4- $\text{H}^{\text{eq}}$ );  
**3**:  $\delta$  1.76 (1H, ddd,  $J = 13.4, 10.2,$  and  $3.2$  Hz, 1- $\text{H}^{\text{ax}}$ ), 1.89-1.93 (2H, m, 5- $\text{H}_2$ ), 2.25 (1H, ddd,  $J = 13.4, 10.3,$  and  $3.1$  Hz, 1- $\text{H}^{\text{eq}}$ ), 2.62-2.75 (3H, m, 4- $\text{H}^{\text{ax}}$  and 9- $\text{H}_2$ ), 2.84 (1H, td,  $J = 11.3$  and  $3.4$  Hz, 8-H), 2.90-2.98 (2H, m, 4- and 8-H), 3.15 (1H, ddd,  $J = 13.4, 10.2,$  and  $3.1$  Hz, 2- $\text{H}^{\text{ax}}$ ), 3.47 (1H, ddd,  $J = 13.4, 10.3,$  and  $3.2$  Hz, 2- $\text{H}^{\text{eq}}$ );

**4:**  $\delta$  1.77 (1H, ddd,  $J = 13.4, 10.1,$  and  $2.9$  Hz,  $1\text{-H}^{\text{ax}}$ ), 1.92-1.96 (2H, m,  $5\text{-H}_2$ ), 2.26-2.34 (1H, m,  $1\text{-H}^{\text{eq}}$ ), 2.55-2.90 (5H, m,  $4\text{-H}^{\text{ax}}$ ,  $8\text{-}$  and  $9\text{-H}_2$ ), 2.93-3.00 (1H, m,  $4\text{-H}^{\text{eq}}$ ), 3.12 (1H, ddd,  $J = 13.4, 10.0,$  and  $7.8$  Hz,  $2\text{-H}^{\text{ax}}$ ), 3.47-3.54 (1H, m,  $2\text{-H}^{\text{eq}}$ );

**6:**  $\delta$  1.55-1.65 (2H, m,  $5\text{-H}_2$ ), 1.87 (1H, td,  $J = 12.6$  and  $5.6$  Hz,  $4\text{-H}^{\text{ax}}$ ), 2.02-2.13 (1H, m,  $4\text{-H}^{\text{eq}}$ ), 2.68 (1H, td,  $J = 10.6$  and  $3.4$  Hz,  $8\text{-H}$ ), 2.77 (1H, ddd,  $J = 15.3, 3.3,$  and  $2.3$  Hz,  $9\text{-H}$ ), 2.80-2.93 (3H, m,  $1\text{-}, 3\text{-},$  and  $9\text{-H}$ ), 2.99 (1H, dd,  $J = 13.7$  and  $6.0$  Hz,  $3\text{-H}$ ), 3.05 (1H, d,  $J = 11.1$  Hz,  $1\text{-H}$ ), 3.13 (1H, ddd,  $J = 10.5, 4.4,$  and  $2.2$  Hz,  $8\text{-H}$ );

**7:**  $\delta$  1.54-1.61 (2H, m,  $4\text{-H}^{\text{eq}}$  and  $5\text{-H}^{\text{ax}}$ ), 1.69-1.80 (1H, m,  $4\text{-H}^{\text{ax}}$ ), 1.97 (1H, bs,  $7\text{-NH}$ ), 2.35 (1H, bd,  $J = 14.0$  Hz,  $5\text{-H}^{\text{eq}}$ ), 2.61 (1H, dd,  $J = 12.6$  and  $1.2$  Hz,  $1\text{-H}^{\text{endo-15}}$ ), 2.65 (1H, ddd,  $J = 15.7, 5.5,$  and  $1.4$  Hz,  $9\text{-H}$ ), 2.74 (1H, ddd,  $J = 15.7, 10.7,$  and  $6.5$  Hz,  $9\text{-H}$ ), 2.99 (1H, d,  $J = 12.4$  Hz,  $1\text{-H}^{\text{egzo-15}}$ ), 3.04 (1H, td,  $J = 13.9$  and  $3.9$  Hz,  $3\text{-H}^{\text{ax}}$ ), 3.18-3.24 (2H, m,  $3\text{-H}^{\text{eq}}$  and  $8\text{-H}$ ), 3.37 (1H, ddd,  $J = 13.6, 10.7,$  and  $5.6$  Hz,  $8\text{-H}$ );

**8:**  $\delta$  1.60-1.70 (3H, m,  $4\text{-H}^{\text{eq}}$ ,  $5\text{-H}^{\text{ax}}$  and  $7\text{-NH}$ ), 1.74-1.85 (1H, m,  $4\text{-H}^{\text{ax}}$ ), 2.42-2.48 (1H, m,  $5\text{-H}^{\text{eq}}$ ), 2.74 (1H, d,  $J = 12.8$  Hz,  $1\text{-H}^{\text{egzo-15}}$ ), 2.80 (1H, ddd,  $J = 15.8, 5.2,$  and  $1.0$  Hz,  $9\text{-H}$ ), 2.91 (1H, bd,  $J = 12.8$  Hz,  $1\text{-H}^{\text{endo-15}}$ ), 2.95 (1H, ddd,  $J = 15.8, 10.8,$  and  $7.0$  Hz,  $9\text{-H}$ ), 3.28 (1H, td,  $J = 13.8$  and  $4.0$  Hz,  $3\text{-H}^{\text{ax}}$ ), 3.34 (1H, ddd,  $J = 13.7, 7.0,$  and  $1.0$  Hz,  $8\text{-H}$ ), 3.52-3.61 (2H, m,  $3\text{-H}^{\text{eq}}$  and  $8\text{-H}$ );

**9:**  $\delta$  1.52 (1H, bd,  $J = 13.0$  Hz,  $5\text{-H}^{\text{ax}}$ ), 1.64-1.72 (2H, m,  $4\text{-H}^{\text{eq}}$  and  $7\text{-NH}$ ), 1.75-1.85 (1H, m,  $4\text{-H}^{\text{ax}}$ ), 2.50-2.55 (1H, m,  $5\text{-H}^{\text{eq}}$ ), 2.69-2.89 (5H, m,  $1\text{-H}, 3\text{-}$  and  $9\text{-H}_2$ ), 3.27 (1H, d,  $J = 12.4$  Hz,  $1\text{-H}$ ), 3.33 (1H, ddd,  $J = 13.7, 4.7,$  and  $1.4$  Hz,  $8\text{-H}$ ), 3.50 (1H, ddd,  $J = 13.7, 10.7,$  and  $5.9$  Hz,  $8\text{-H}$ );

5. The force field and the MNDO calculations were conducted using the SYBYL 5.51 integrated package (Tripos), installed on ESV 10/33 workstation.
6. Ionization constants were determined by a potentiometric titration of **1**·2HCl at  $20 \pm 0.5$  °C.
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